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Application No: 10/781,047
Amendment dated June 3, 2008
Amendment in Response to Non-Final Office Action

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REMARKS

Claims 6-22 and 25 are currently pending in this application. Claim 6 has been amended in this Amendment. Support for the amendment can be found throughout the specification as filed, for example, page 27, lines 13-18 and page 28, lines 11-18. No new matter has been added.

1. Claims 6-22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desiderio (J Chromatography B 1999;731:3-21) in view of Gerber et al. (Anal. Chem. 2001, 73:1651-1657).

The Examiner states, "Desiderio teaches a method for determining the presence/quantity of a target polypeptide in a mixture of different polypeptides by providing a mixture of human tissue extracts (from human with metabolic defects and normal control-page 5, 2.1 and 2.2), adding two known quantity of labeled (labeled differently with stable isotopes) peptide internal standard (page 5, 2.4), treating the mixture with a protease (trypsin-page 7, 2.6), fragmenting the peptides in the mixture by multistage mass spectrometry (tandem mass spectrometer-page 7, 2.8), determining the ratio of labeled fragments to unlabeled fragments and calculating the quantity of the target polypeptide in the mixture (page 7, 2.10.1 and page 8, 2.10.2). Peptides are separated by HPLC chromatograph (page 6, under Chromatograph, 2.5.1-2.5.4) and the fractions (eluent and co-eluent) are shown in Fig. 5-7. The presence/quantity of target polypeptide is diagnostic of a cell state where the cell state is representative of an abnormal physiological response (human pituitary macroadenomas-page 9, 3.1), and the target polypeptide is determined in at least two mixtures (abstract and for details see pages 9-14, pages 14-17).

Desiderio does not teach a single peptide internal standard in the method.

Gerber teaches a chromatography/mass spectrometry method for determining multiple enzyme activities in human cell lysates using a single internal standard (page 1652, right column, 2nd full paragraph). Gerber also teaches that the internal standard is chemically identical to the enzyme product and contain isotope (page 1652, right column, 2nd full paragraph, lines 4-7).

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Desiderio by using a single peptide internal standard in the method because protease activity is used and Gerber teaches the use of a single internal standard which is identical to the enzyme product (peptide as the product of protease) in the same chromatography/mass spectrometry method. One would have been motivated to make the modification because Desiderio et al. specifically described a method for determining the presence/quantity of a target polypeptide in a mixture of different polypeptides with two peptide internal standard, and would reasonably have expected success because Gerber teach the use of an internal standard that is chemically identical to the enzyme product in the same method (page 1652, right column, 2nd full paragraph). One internal standard is recognized as equivalent of two internal standard for the same purpose (see MPEP §2144.06), thus using one internal standard that is chemically identical to the enzyme product as taught by Gerber for the predictable result of determining the presence/quantity of a target peptide is obvious."

Applicants respectfully disagrees. It is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

There is no suggestion or motivation in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the cited reference to make the claimed invention, nor is there a reasonable expectation of success. Most importantly, the Desiderio and Gerber references do not teach or suggest all of the claim limitations. In

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particular, neither the Desiderio or Gerber references teach or suggest the use of proteolysis of the labeled peptide internal standard and any target peptide (see step [C] of claim 6 from which all other claims depend). In addition, neither the Desiderio or Gerber references teach or suggest the measurement of target peptides and modified target peptides.

The Applicants' invention make use of the knowledge of how peptides behave in a mass spectrometer to select a peptide or peptides to monitor after proteolysis (a step required by the claims, but not mentioned or cited in the Desiderio or Gerber references). In addition, the Applicants go one step further to monitor posttranslationally-modified proteins (such as by phosphorylation or acetylation). Using synthetic peptides containing stable isotopes identical to both the modified and unmodified forms of the peptide sequence from the protein of interest, Applicants can find out the occupancy state of that modification on the protein.

Furthermore, with regard to the Gerber reference, this prior art document has nothing to do with the present invention. They are measuring enzyme activities by measuring the amount of product formation. There is nothing here about measuring protein levels or the amount of a modification on a protein. Gerber demonstrates the method on heparin-modifying enzymes by creating internal standards of sulfated polysaccharides (not proteins).

Therefore, the Desiderio and Gerber references cannot be cited as a basis for an obviousness rejection of claims 6-22 and 25 in the present application. Applicants respectfully request reconsideration.

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In view thereof, reconsideration and withdrawal of the §103 rejections are requested.


Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. Applicant's representative would like to discuss this case with the Examiner to learn if any outstanding issues remain after consideration of this Amendment. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record. The Applicants believe that a one-month extension of time is required.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Dated: June 4, 2007

Respectfully submitted,

By 
Gregory B. Butler, PhD, Esq.
Registration No.: 34,558
EDWARDS ANGELL PALMER & DODGE
LLP
P.O. Box 55874
Boston, Massachusetts 02205
617-517-5595
Attorneys/Agents For Applicant